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Confirmation of Early Menopause in Fragile X Carriers

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Fragile X carriers have a median age of menopause 6 to 8 years earlier than women in the general population, with 28% experiencing premature ovarian failure defined as menopause before the age of 40 years. This information was obtained from 203 returned questionnaires from women in the UK Fragile X Society. © 1996 Wiley-Liss, Inc.

KEY WORDS: menopause, premature ovarian failure, fragile X syndrome, twinning

INTRODUCTION

For many years clinicians have observed that the menopause comes early in some families with the fragile X syndrome. Schwartz et al. [1994] documented this in a multicentre survey in the United States in which it was found that 19% of 176 fragile X carriers had premature ovarian failure (POF) meaning that they had reached the menopause by the age of 40 years compared with 1.6% of their controls. We have confirmed these findings in fragile X carriers in the United Kingdom.

MATERIAL AND METHODS

A simple questionnaire was sent out to 454 women in the UK Fragile X society who had agreed, on joining the Society, to participate in research. Questions were asked about their carrier status whether by position in the family pedigree, cytogenetic or DNA tests and, if menstrual periods had stopped, at what age. Similar information was requested about other known carriers in their families. This produced two groups of data, one from the carriers themselves and one from their carrier relatives.

Two hundred forty replies were received (52.8%). Of these 14 were excluded because of inadequate information and another 23 because menstruation had been stopped by hysterectomy leaving 203 questionnaires for analysis. The average age of these women was 41.3 (median 40) with a range of from 22 to 74 years.

RESULTS

Table I and Figure 1 show the age of menopause in the two groups of fragile X carriers compared with published data for English women [Frommer, 1964; McKinley et al., 1972; Gray, 1976]. The distributions of menopausal ages in both groups of carriers were negatively skewed. The medians and means of both groups were 6–8 years below those published for English women; the differences in both mean ages were more than 5 times their standard errors. All these differences are highly significant statistically. The proportion of women reporting menopause below the age of 40 years was 28% in both groups of carriers.

DISCUSSION

Recollected data gathered by mailed questionnaires have several obvious biases. It was possible to test for two of these which have been stressed by both Frommer [1964] and Gray [1976] as significant. The first is a tendency for women to "round off" their age of menopause in retrospect to numbers with the nearest 0 or 5, thus giving an excess of ages such as 35, 40, or 45. There was no evidence of this in the present data (Fig. 1). The second bias is for "women who are more than 5 years postmenopausal consistently to underestimate their age at menopause" [Gray, 1976]. This was not found in our group of 49 carriers. Their post-menopausal ages ranged from 1 to 35 (median 8 years); the correlation coefficient between age of menopause and years after it was reported was not significant ($r = -0.117$; $P > 0.1$). It was not possible to tell whether those women who had had an early menopause were more likely to return the questionnaire. However, if this were the case it would have to be inferred that such women were more likely to report those relatives who also had an early menopause. This is possible but unlikely, but further studies are planned which will take this possible bias into account. We think that the consistent findings in the carrier women and their relatives and the magnitude of the differences in the median ages of menopause from English women in general are good evidence for early menopause in fragile X carriers. It should be stressed that although the data for English women

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TABLE I. Ages of Menopause in Fragile X Carriers

	Carriers	Carrier relatives	English women: McKinley et al. [1972]*	English women: Frommer [1964]
Number of women	49	57	653	154
Age of menopause (yr)				
Mode	43	44	—	50.1
Median	43	44.16	50.78	50.1
Mean	42.60	41.90	47.49	—
Standard deviation	6.26	8.0	5.39[a]	—
Standard error	0.89	1.06	0.211	—
Range	28–54	27–53	—	—
Menopause <40 years				
Number	14	16	—	—
Percentage	28.6	28.1	—	—

* Age range confined to 45–54 years.
[a] Calculated.

were collected 20 to 30 years ago there is no evidence for a secular change in menopause over the past 100 years as there is for menarche [McKinley et al., 1972; Gray, 1976].

An early menopause in the fragile X syndrome is supported by the work of Black et al. [1995] who found that 8 out of 9 fragile X carriers below the age of 34 years had decreased ovarian responses to exogenous stimulation and 4 had perimenopausal FSH levels. Further evidence comes from Conway et al. [1995] who found that 2 of 9 women with familial premature ovarian failure had fragile X premutations. The information in the present survey did not allow differentiation between those carriers with full mutations and those with premutations: in this population one would expect the ratio to be 1:3.5. Only those with full mutations would be expected to have reduced FMR1 protein and show phenotypic effects (e.g., mental retardation); those with premutations

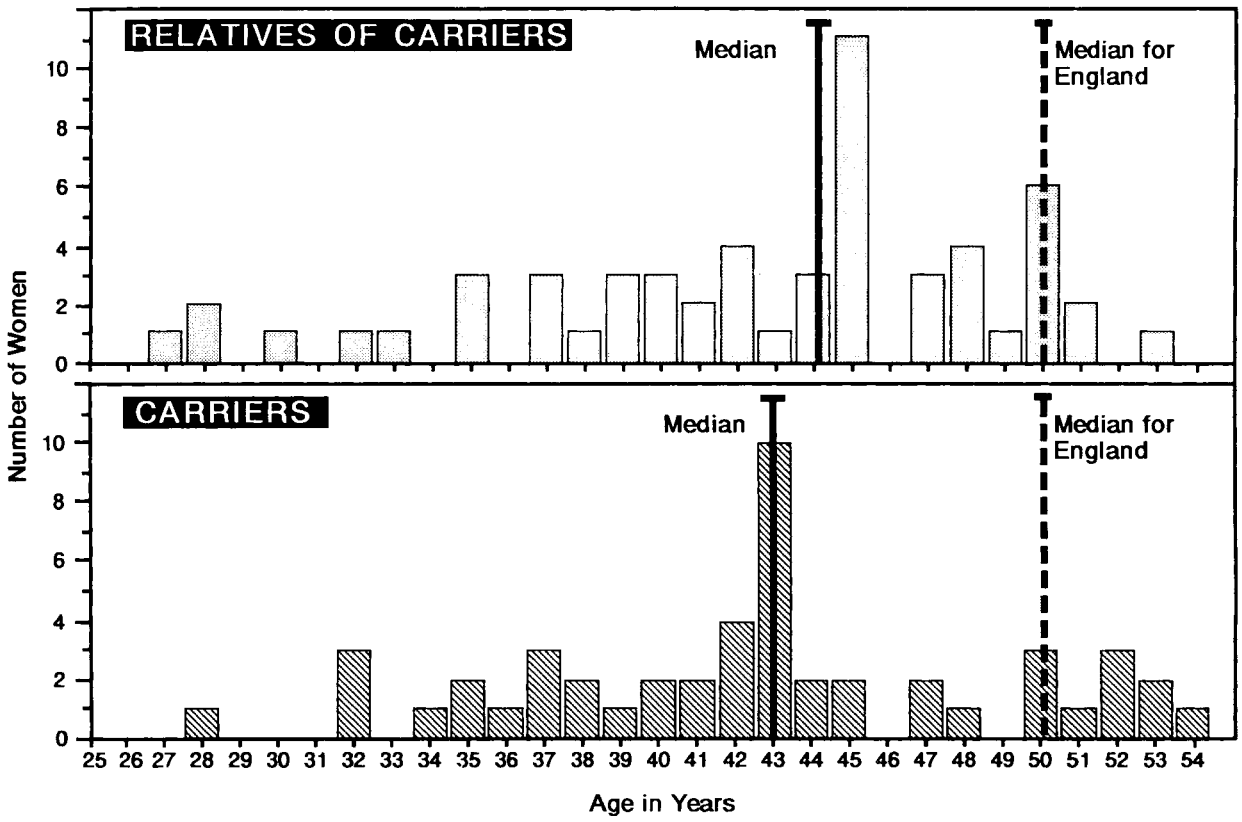

Fig. 1. Age of menopause in carriers and relatives of carriers of the fragile X syndrome. Medians indicated together with the median for English women.

should be phenotypically normal. However, Schwartz et al. [1994] found that early menopause was confined to premutation carriers. Furthermore the observed increase in dizygous (DZ) twinning also appears to be confined to the premutation group [Turner et al., 1994].

It is known that DZ twinning rates increase with age peaking at 35 years with a subsequent sharp decline. DZ twinning at 35 is associated with a hormonal profile reflecting declining numbers of follicles in the ovary and excess hypothalamic stimulation. Fragile X carriers may produce fewer eggs in utero leading to earlier ovarian failure [Conway et al., 1995] with a shift to the left of the peak DZ twinning rate and more twins born because the women are younger. Alternatively, the excess of DZ twinning could reflect a programmed excess hypothalamic stimulation of the ovaries resulting in excess follicular usage and earlier menopause.

The findings of POF and increased DZ twinning in fragile X carriers is fascinating and suggests that an increase in trinucleotide repeats has some effects that are different from those seen when the amplification is sufficient to induce methylation and gene silencing.

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